REMARKS

Claims 1-4 are pending and currently amended.

Independent claim 1 has been amended to recite a "method to distinguish" rheumatoid arthritis (RA) from osteoarthritis (OA). Support for the amendment is found in Table 2 of the specification wherein the data distinguishes rheumatoid arthritis (RA) from osteoarthritis (OA) based on the differential expression of WNTs and FRPs. Dependent claims 2-4 are amended in conformance with claim 1.

Claims 3 and 4 have been amended to replace the typographical error of "inhabitation" with "inhibition" and to replace "FRP" with "FRP1". Support for "FRP1" is found at page 6, line 4 of the specification.

No new matter within the meaning of § 132 has been added by the amendments.

A § 1.132 declaration by the first named inventor, Kazushi Imai, is provided showing enablement of the invention.

Accordingly, it is respectfully requested that a Notice of Allowance be issued in the captioned application.

1. **Rejection of Claims 1-4 under 35 U.S.C. § 112, ¶ 1 enablement**

The Office Action rejected claims 1-4 under 35 U.S.C. § 112, ¶ 1 as containing subject matter which was not described in the specification in such a way as to *enable* one skilled in the art to make and/or use the invention.

(1) Quantity of Experimentation

The Office Action alleged that the quantity of experimentation in this area is large because there is a significant number of parameters which would have to be studied such as comparative studies of RA and normal (and not RA and OA as disclosed in the specification) of WNT10b, and any FRP1, 2, 3, 4, or 5 in joint synovial fluid, synovial tissues and peripheral blood.

The quantity of experimentation for the claims as amended is sufficient because they recite a "method of distinguishing RA from OA". The data distinguishes rheumatoid arthritis (RA) from osteoarthritis (OA) based on the differential expression of WNTs and FRPs. Peripheral blood is deleted and FRP1 is the only claimed frizzled protein.

Regarding normal control synovium, a § 1.132 declaration is submitted showing immuno-staining on five normal synovial tissues obtained from individual patients with hip fracture. The immuno-stain shows that all proteins (WNT10B, FRP1 and β-catenin) were negatively stained in normal synovium. See attached § 1.132 declaration.

(2) Guidance in the Specification

The Office Action alleged that the specification provides no evidence regarding the upregulation of WNT10B expression in synovial fluid, synovial tissue and in peripheral blood and instead teaches RT-PCR comparisons in 5 RA and 4 OA tissues and not RA to normal tissues and further alleged that the results in Table 2 showing WNT10B and FRPs is not upregulation or inhibition because upregulation requires a quantitative change.

Peripheral blood is deleted and FRP1 is the only claimed frizzled protein.

In a peer reviewed article, WNT family members are described as being "upregulated" in RA synovium. See "Differential Expression of WNTs and FRPs in the synovium of rheumatoid arthritis and osteoarthritis", *Biochem. And Biophy. Res. Comm.*, Imai *et al.*, 345, page 1615-1620 (2006) (copy attached). WNT signaling and WNT target gene expression are specifically activated in RA synovium because biological actions of WNT signaling are compatible with aggressive features of RA synovium, *i.e.*, enhanced cell proliferation, tissue remodeling and angiogenesis, and production of inflammatory cytokine expression. The data and conclusions were reviewed by scientific referees and similar to that of the instant specification showed a predominant expression of WNT10B by RT-PCT (5/7 cases) and immuno-staining (16/16 cases) in RA synovium contrasted to negligible expression in OA synovium (2/7 cases by RT-PCR and 6/14 cases by immuno-staining).

(3) Working Examples

The Office Action alleged that the specification contained no working examples of detecting RA by detecting upregulation of WNT10b and inhibition of FRPs in synovial fluid, synovial tissue and in peripheral blood. The position was that the specification only disclosed a trend toward RA having more cases of WNT10b expression and less of FRP1 RT-PCR positive synovium samples when compared to OA.

The amended claims are sufficient because the data in the specification distinguish RA from OA. The claims recite a "method of distinguishing RA from OA" while the data distinguishes rheumatoid arthritis (RA) from osteoarthritis (OA) based on the differential expression of WNTs and FRPs. Peripheral blood is deleted and FRP1 is the only claimed frizzled protein.

(6) Level of Skill in the Art

The Office Action asserted that the level of skill in the art is deemed to be high for the claimed invention. Nonetheless, the amended claims are enabled by the specification.

(5) and (7) The unpredictability of the art and the state of the prior art

The Office Action asserted that the prior art teaches that synovium can be used to detect specific mRNAs using RT-PCR technique where synovium contains a unique population of synovial lining cells in RA and osteoarthritis (OA) that appear to be

activated in WNT signaling phenotypes. *Citing Nakamura et al.*, 2005, American Journal of Pathology, 167:97-105, page 97, right column, ¶ 2.

Nonetheless, the amended claims are enabled by the specification. The claims as amended recite a "method of distinguishing RA from OA" while the data distinguishes rheumatoid arthritis (RA) from osteoarthritis (OA) based on the differential expression of WNTs and FRPs. Peripheral blood is deleted and FRP1 is the only claimed frizzled protein.

(8) The nature of the invention and breadth of claims

The Office Action noted that the claimed invention is in a class of invention which the Federal Circuit has characterized as "the unpredictable arts such as chemistry and biology." *Citing Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001). Despite the broad and general assertion, the amended claims are enabled by the specification.

2. **Rejection of Claims 1-4 under 35 U.S.C. § 112, ¶ 2**

The Office Action rejected claims 1-4 as being indefinite. The Office Action stated:

> The terms "upregulation" in claims 1-2 is a relative terms which renders the claim indefinite. The term "upregulation" is

> not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.
>
> Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.,* 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "inhabitation" in claims 3 and 4 is used by the claim to mean "inhibition while the accepted meaning is "living or being present." Applicant is reminded no new matter may be added.

It is respectfully submitted that the term "upregulation" particularly points out and distinctly claims the subject matter of the invention. One of ordinary skill in the art would know that WNT family members are "upregulated" in the RA synovium because WNT signaling and WNT target gene expression are specifically activated in RA synovium; and because biological actions of WNT signaling are compatible with aggressive features of RA synovium, *i.e.*, enhanced cell proliferation, tissue remodeling and angiogenesis, and production of inflammatory cytokine expression.

In a peer reviewed article authored by the first named inventor, WNT family members are described as being "upregulated" in the RA synovium for similar data. See "Differential Expression of WNTs and FRPs in the synovium of rheumatoid arthritis and osteoarthritis", *Biochem. And Biophy. Res. Comm.*, 345, page 1615-1620 (2006)

(copy attached). One of ordinary skill in the art would be reasonably apprised as to the meaning of "upregulation" as used in the claims given that the article has been peer reviewed by scientific referees versed in the art.

Claims 3 and 4 have been amended to replace the typographical error of "inhabitation" with "inhibition".

3. **Rejection of Claims 1-4 under 35 U.S.C. § 112, ¶ 1 written description**

The Office Action rejected claims 1-4 as containing subject matter that was not described in the specification. The Office Action stated:

> With respect to claims 1 and 2 which encompass detection of "at least the upregulation of expression of WNT10B" the current claims encompass a large genus of nucleic acids which comprise any WNT10B, which encompasses all splice variants and mutants. Similarly, with respect to claims 3 and 4 which encompass "inhabitation of expression of FRP", the current claims encompass a large genus of nucleic acids which comprise any FRP, which encompasses, FRP1-5 and any frizzled related proteins. The genus includes an enormous number of variants, and combinations for which no written description is provided in the specification. This large genus, is not represented in the specification.

It is respectfully submitted that claims 1 and 2 as amended adequately support the claimed limitation of "at least the upregulation of expression of WNT10B".

Although the Office Action alleged that the limitation encompasses a large genus

of nucleic acids which comprise any WNT10B encompassing all splice variants and mutants, the limitation clearly recites "WNT10B" wherein the WNT family covers 19 known paralogues in the human genome. See Capon v. Eshhar, 418 F.3d 1349, 1360 (Fed. Cir. 2005) (holding that not all the permutations and combinations covered by the claims are required if well known in the art).

Primer sequences for all members of the WNT family (19 paralogues) have been previously described. See Uraguchi *et al.* "Activation of the WNT family expression and signaling in squamous cell carcinomas of the oral cavity", J. *Dent. Res.* 83 (2004) 234.1-234.7 (copy attached). Hence, the limitation of WNT10b is adequately supported.

Regarding claims 3 and 4, as amended, they recite "FRP1" rather than "FRP".

4. **Rejection of Claims 1-4 under 35 U.S.C. § 102(b)**

The Office Action rejected claims 1-4 as being anticipated by Sen *et al.*, 2000, PNAS, 97:2791-2796. The Office Action stated:

> Sen teaches detection of Wnt10b by RT-PCR in 5 RA and 5 OA synovial tissue samples, where 3/5 RA and 2/5 samples show Wnt10b signal. Because more RA samples show positive Wnt10b than OA samples, the claims are broadly construed to encompass this since RA has upregulated Wnt10b expression.
>
> Claims 3 and 4 are directed to FRP which is broadly interpreted as any protein that is related to frizzle. Therefore

> FRP encompasses frizzle family protein including frizzle 2 and frizzle 5. Sen teaches RT-PCR detection of fz2 and fz5 along with Wnt10b. Therefore Sen teaches each of the limitations of claims 1-4, namely detection by RT-PCR of Wnt10b and frizzled related protein simultaneously to detect whether a person has RA.

It is respectfully submitted that Sen *et al.* fails to establish a *prima facie* case of anticipation because it does not expressly or inherently teach the presently claimed method of distinguishing RA from OA.

Contrary to the characterization in the Office Action, Sen *et al.* teaches that there is **no** differential expression of WNT10b between OA and RA. See Table 1. The symbol "+/-" is used in Sen *et al.* to show that three to four specimens were detected. In Table 1, Sen *et al.* shows the same symbol "+/-" for both OA and RA for WNT10b.

Sen *et al.* also fails to provide an enabling disclosure and is inoperable with respect to the claimed invention because Sen *et al.* teaches that the data relied upon for gene expression came from frozen specimens. However, freezing tissue causes decomposition of RNA.

In contrast, the present invention relies on total RNA isolated from patients according to the Chomczynski and Sacchi method where RNA is immediately and directly sampled from freshly removed tissue. See "Single-Step Method of RNA isolation by acid guanidium thiocyanate-phenol-chloroform extraction", Chomczynski *et al.*, Analy. Biochem. 162, 156-159 (1987) (reference attached). Given the very different methods of preparation and analysis, undue experimentation is required to make the

claimed method. See Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

Regarding amended claims 3 and 4, Sen *et al.* fails to provide any teaching of FRP1. Hence, there is no anticipation.

CONCLUSION

In light of the foregoing, the application is now in condition for allowance. It is therefore respectfully requested that the rejection(s) be withdrawn and the application passed to issue.

Respectfully submitted,

HAHN & VOIGHT PLLC

Attorney for Applicants
Roger C. Hahn
Reg. No. 46,376

HAHN & VOIGHT PLLC
1012 14TH Street, N.W.
Suite 620
202-637-0020